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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/640,989	08/14/2003	Lijun Yang	5853-261	9213

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BARNHART, LORA ELIZABETH

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/640,989	YANG, LIJUN	
	Examiner Lora E. Barnhart	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 15 July 2005.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 2-7, 10, 11 and 14-24 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1, 8, 9, 12 and 13 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5/4/04, 1/18/05</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |



DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1, 8, 9, 12, and 13, in the reply filed on 7/15/05 is acknowledged. Claims 2-7, 10, 11, and 14-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Examination will continue at this point on claims 1, 8, 9, 12, and 13 ONLY.

Claim Objections

Claim 1 is objected to because of the following informalities: It recites the Latin phrase "in vitro", which should be italicized: "*in vitro*". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 8 and 9 are drawn to a cell "wherein the cell is comprised in a liquid", which is confusing. Language such as, "A composition comprising the cell of claim 1 and a liquid" is preferred.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 8, and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Ramiya et al. (2002, U.S. Patent Application Publication 2002/0182728; reference A). The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium.

Ramiya et al. teach human bone marrow stem cells that express insulin after 45 days of growth in cell culture medium (paragraphs 0032 and 0059-0061; Figure 1).

Claims 1, 8, and 9 are also rejected under 35 U.S.C. 102(e) as being anticipated by Black et al. (2003, U.S. Patent Application Publication 2003/0104997; reference B). The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium.

Black et al. teach human bone marrow cells that express insulin in cell culture medium (paragraphs 0057-0061, 0067, and 0102-0108).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (1998, *Chinese Medical Journal English Edition* 111: 899-902; reference U) taken in view of Kuznetsov et al. (1997, *Journal of Bone and Mineral Research* 12:1335-1347; reference V). The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium.

Wang et al. teach cultures of mouse Ltk- fibroblasts stably transfected with the human insulin gene; the clonal lines expressed high levels of insulin even after 6 weeks of culture (page 900, column 1, paragraph 2; page 900, column 2, paragraph 1; and Table). Wang et al. do not teach transfection of human bone marrow cells.

Kuznetsov et al. teach that human bone marrow comprises stromal fibroblasts (HMSFs; see Abstract and pages 2, 3, 6, and 7).

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A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the HMSFs of Kuznetsov et al. into the transfection protocol of Wang et al. because both cell lines are fibroblasts. The skilled artisan would have been motivated to make said substitution for the expected benefit that human cells are better suited for later transplantation into humans.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to transfet the HMSFs of Kuznetsov et al. with the human insulin gene construct of Wang et al. because Wang et al. teach that said construct can be transfected into and expressed by mammalian fibroblasts. The selection of fibroblast type and source clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Wang et al. teach that said construct can be transfected into and expressed by mammalian fibroblasts. A holding of obviousness over the cited claims is therefore clearly required.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 1, 8, 9, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Ramiya et al. (reference A) or Black et al. (reference B) taken in view of Boyse et al. (1991, U.S. Patent 5,004, 681; reference C), Polovina (1996, U.S. Patent 5,580,714; reference D), and Gianni (1997, U.S. Patent 5,649,904; reference E). The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture

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medium. In some dependent claims, the cells are stored at a temperature below freezing, optionally in liquid nitrogen.

As discussed above, Ramiya et al. and Black et al. each teach a culture of human bone marrow cells that express insulin. Neither Ramiya et al. nor Black et al. teach freezing the cells.

Procedures for cryopreservation of mammalian cells in liquid nitrogen are known in the art. For example, Boyse et al. teaches that human bone marrow cells can be successfully recovered from long-term storage in liquid nitrogen (column 7, lines 1-4). Gianni teaches that techniques of bone marrow procurement, leukapheresis, and freezing are standard in the art (column 5, lines 36-39). Polovina teaches that stem cells are capable of withstanding cryopreservation and thawing (column 4, lines 16-18) and provides one method for performing the same (column 8, lines 5-10).

A person of ordinary skill in the art would have had a reasonable expectation of success in cryopreserving the cells of Ramiya et al. or Black et al. in liquid nitrogen because Boyse et al. and Polovina teach that techniques for the same are well known and that bone marrow cells are not destroyed by freezing and thawing. The skilled artisan would have been motivated to cryopreserved the cells of Ramiya et al. or Black et al. for the expected benefit that the insulin-producing cells could be cultured on a large scale, then frozen in small aliquots for controlled thawing and use in downstream applications.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the cells of Ramiya et al. or Black et al.

because Boyse et al., Polovina, and Gianni teach that such a procedure is well known in the cell culture art.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 1, 8, 9, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. taken in view of Kuznetsov et al. as applied to claims 1, 8, and 9 above, and further in view of Boyse et al., Polovina, and Gianni. The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium. In some dependent claims, the cells are stored at a temperature below freezing, optionally in liquid nitrogen.

As discussed above, Wang et al. teach cultures of mouse Ltk- fibroblasts stably transfected with the human insulin gene; the clonal lines expressed high levels of insulin even after 6 weeks of culture. Wang et al. do not teach cryopreservation of human bone marrow cells.

Kuznetsov et al. teach that human bone marrow comprises stromal fibroblasts. Procedures for cryopreservation of mammalian cells in liquid nitrogen are known in the art. For example, Boyse et al. teaches that human bone marrow cells can be successfully recovered from long-term storage in liquid nitrogen (column 7, lines 1-4). Gianni teaches that techniques of bone marrow procurement, leukapheresis, and freezing are standard in the art (column 5, lines 36-39). Polovina teaches that stem cells

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are capable of withstanding cryopreservation and thawing (column 4, lines 16-18) and provides one method for performing the same (column 8, lines 5-10).

A person of ordinary skill in the art would have had a reasonable expectation of success in cryopreserving the cells of Wang et al. taken in view of Kuznetsov et al. in liquid nitrogen because Boyse et al. and Polovina teach that techniques for the same are well known and that bone marrow cells are not destroyed by freezing and thawing. The skilled artisan would have been motivated to cryopreserved the cells of Ramiya et al. or Black et al. for the expected benefit that the insulin-producing cells could be cultured on a large scale, then frozen in small aliquots for controlled thawing and use in downstream applications.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the cells of Wang et al. taken in view of Kuznetsov et al. because Boyse et al., Polovina, and Gianni teach that such a procedure is well known in the cell culture art.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart, whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn, can be reached on 571-272-0926. The fax phone

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number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lora E Barnhart

Leb



SANDRA E. SAUCIER
PRIMARY EXAMINER